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(57) Abstract

Use of doxepin, doxepin hydrochloride or a metabolite of doxepin or doxepin hydrochloride for the manufacture of a medicament for ameliorating pain in an individual.

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TOPIC TRICYCLIC ANTIDEPRESSANTS AS ANALGESICS

Description

The present invention relates to the use of tricyclic antidepressants (TCAs), particularly doxepin, doxepin hydrochloride and its metabolites, as topically applicable analgesics.

Tricyclic antidepressants (TCAs) are a class of antidepressants which are generally prescribed to individuals suffering from depression and are usually formulated for oral administration. There are at least 28 different compounds which fall under the definition of TCAs (see The Merck Index, 12th Edition, page "THER-8"). In addition to their use in the treatment of depression, a number of TCAs have also been proven to be effective, when administered orally, in providing an analgesic or pain-relieving effect particularly in the treatment of neuropathic pain [1].

Neuropathic pain refers to pain resulting from a disease which affects the function of one or more peripheral nerves. The disease, peripheral neuropathy, may be restricted to the peripheral nervous system, involve both the peripheral and central nervous system, or affect multiple organ systems. Peripheral neuropathies can be encountered in all age groups and may be hereditary or acquired, with diverse causes including diabetes, HIV infection and cancer. The resulting pain may be acute (lasting days), sub-acute (weeks) or chronic (months or years) (see Pathology, 2nd Edition, Rubin & Faber, J.B. Lippincott & Co. 1994)

Evidence exists for the pain relieving effect of TCAs, when administered orally, in neuropathic pain, with a broad spectrum of these agents including Amitriptyline [2,3,4,5,8,13,16], Imipramine [11,15], Desipramine [6,7,8,9,12] and Clomipramine [9,10,14]. This analgesic effect is independent of their antidepressant properties [2,3] and is not associated with changes in peripheral and autonomic nerve function [9]. The effect of TCAs are not replicated by the other classes of antidepressants. There appears to be a relationship between plasma level of the TCA and therapeutic effect [9].

However, the use of TCAs is often complicated by side effects, with such effects being almost as common as therapeutic effect (numbers needed to treat (NNT) for intended effect between 2.3 and 3 depending on condition, NNT for side effects 3.7, [1]). Common side effects experienced with taking these drugs orally include drowsiness, asthenia, increased appetite, dry mouth, diarrhoea, dyspepsia and headache. Patients are therefore often reluctant to take a dose sufficient to achieve substantial pain relief due to the side effects produced. Moreover, such side effects may discourage the use of these compounds in patients requiring long term treatment. Thus, it would be desirable to use TCAs in a formulation in which the therapeutic effects could outweigh the undesirable side effects.

Doxepin is a dibenzoxepin derivative and is one TCA belonging to the group of dibenzoxepin tricyclic compounds (see Merck Index, 12th Edition, compound no. 3492). It is generally produced as an isomeric mixture of both its cis and trans isomers. Its hydrochloride salt, doxepin hydrochloride (1-propanamine, 3-dibenz(b,e)oxepin-11 (6H)ylidene-N,N-dimethyl-, hydrochloride), has a molecular formula $C_{19}H_{21}NO.HCl$ and a molecular weight of 316.

When taken orally, doxepin is absorbed into the systemic circulation and undergoes hepatic metabolism that results in conversion to a number of metabolites, with the principle active metabolite being desmethyldoxepin. However, a number of side effects are seen in patients taking doxepin orally, drowsiness being most commonly observed.

In addition, doxepin hydrochloride has been formulated as a cream suitable for topical application for use as an antipruritic in conditions such as eczema (eczematous dermatitis, atopic dermatitis and lichen simplex chronicus). For example, a 5% cream (Xepin cream, available from Bioglan Laboratories, Hitchin, Hertfordshire, England) has recently been released in the UK with a product licence for relief of pruritis (itching) associated with eczema. Generally, the topical cream is indicated for the short-term (up to 8 days) management of moderate pruritis. The exact mechanism by which doxepin exerts its antipruritic effect is unknown.

Thus, the use of doxepin or doxepin hydrochloride both as an orally administered antidepressant and topically in the treatment of pruritis is recognised. However there has, so far, been no suggestion that doxepin can exert any analgesic effect whether administered either orally or as a topical preparation.

In a first aspect, the present invention provides the use of doxepin, doxepin hydrochloride or a metabolite of doxepin or doxepin hydrochloride in the preparation of a medicament for ameliorating pain in an individual.

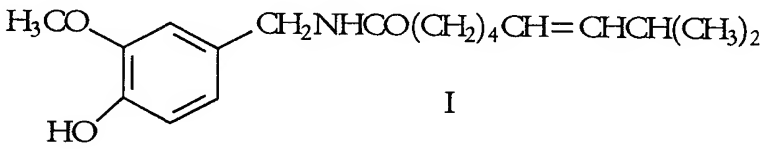
Where doxepin, doxepin hydrochloride or their metabolites are referred to, it is to be understood to include both the cis and trans isomers of doxepin or doxepin hydrochloride and isomeric mixtures of the same, any other salts of doxepin and their metabolites including the primary active metabolite, desmethyldoxepin.

Where medicaments prepared in accordance with the invention are said to ameliorate or to be for ameliorating pain, it is meant that they are effective to reduce the intensity of pain, or have an analgesic effect, and, although a so described agent is preferably capable of eliminating a particular pain, it need not necessarily be capable of so doing. The term pain is used in a general sense and is intended to encompass pain levels between the merely uncomfortable and the virtually unbearable.

In a second aspect, the present invention provides the use of a tricyclic antidepressant or TCA in the preparation of a medicament for ameliorating pain in an individual, wherein the medicament is formulated for topical application.

Where the term TCA is used it incorporates all tricyclic antidepressants. This class of compounds includes at least 28 different compounds (see The Merck Index, 12th Edition, page "THER-8"). Thus, in a preferred embodiment, the TCA is amitriptyline, imipramine, desipramine or clomipramine. Preferably the TCA is doxepin, doxepin hydrochloride or their metabolites.

In this application, the present inventor has demonstrated for the first time an analgesic effect of the topically applied TCA, doxepin, in chronic human neuropathic pain [25]. With a clinical impression of a synergistic effect when agents from different classes of drugs are co-administered, it was decided to examine the effect of topical administration of capsaicin, doxepin and a mixture of both on chronic human neuropathic pain. Capsaicin, whose use as an analgesic was described as long ago as 1850 [17], has a verified analgesic effect in the pain of post herpetic neuralgia [18,19,20], diabetic neuropathy [21,22] and surgical neuropathic pain [23]. Capsaicin my be represented by the general formula I



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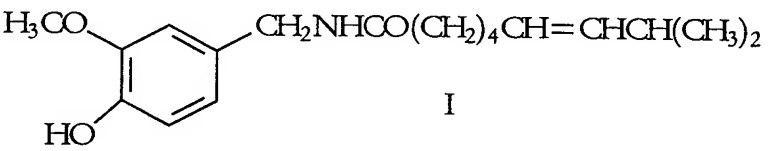
Capsaicin causes release of substance P from C fibre afferent neurones, and repeated application reversibly depletes stores of substance P and therefore reduces pain transmission from peripheral nerve fibres to higher centres [24]. Surprisingly, it was found that, whilst overall pain was significantly reduced by doxepin, capsaicin and a doxepin/capsaicin mixture to a similar extent, the analgesia with the doxepin/capsaicin mixture was of more rapid onset. The onset of analgesia with doxepin/capsaicin mixtures became apparent in some cases within 1 week of commencing treatment, compared to as much as 2 weeks with doxepin alone.

In a third aspect of the invention, there is provided the use of a TCA and a compound of formula I



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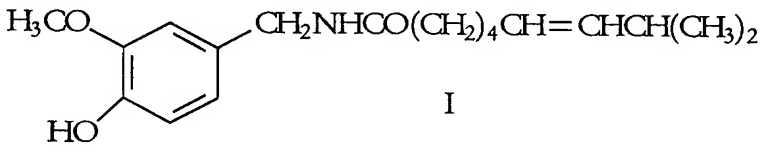
for the manufacture of a medicament for ameliorating deep seated or internal pain or discomfort in an individual, wherein the TCA has an ameliorating effect upon said pain.

In a fourth aspect of the invention, there is provided a pharmaceutical composition comprising a TCA and a compound of formula I:



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In a fifth aspect of the invention, there is provided a pharmaceutical composition according to the invention in its fourth aspect, for use as an analgesic.

In a preferred embodiment of the invention in its fourth and fifth aspects, the TCA is present in the pharmaceutical composition in an amount sufficient to reduce burning discomfort associated with the application of a compound of formula I to the skin. Preferably, the compound of formula I is present in an amount sufficient to augment an analgesic effect provided by the TCA.

In preferred embodiments of the invention in any of its various aspects, the medicament further comprises a pharmaceutically active carrier rendering it suitable for topical application, preferably to the skin. Preferably, the medicament is a cream, jelly or ointment. Suitable carriers are well known to those skilled in the art. Suitable carriers include those employed in Xepin cream available from Bioglan Laboratories Ltd. These can include a base cream of pH3.5-5.5 that includes the inactive ingredients: sorbitol, cetyl alcohol, isopropyl myristate, glyceryl stearate, PEG-100 stearate, petrolatum, benzyl alcohol, titanium dioxide and purified water.

Preferably, the medicament for use in accordance with the invention is formulated for topical application at or in the vicinity of the source of pain or the perceived origin of the pain (even if, in reality it is more central).

In general, patients prefer topical preparations of pain-relieving compounds to oral ones. In particular, patients like the notion that they can apply the medication to the site they perceive the pain to be originating from (even if in reality it is more central). Furthermore, it is desirable for the beneficial effects of a compound to be harnessed while reducing the side effects experienced by the patient. By applying a topical preparation, patients would experience less severe side effects to those experienced upon taking the amount of TCA in an oral formulation which would be sufficient to elicit an analgesic effect. In view of the reduced side effects, a topical preparation can be used over a longer time period and therefore in the treatment of chronic or long lasting pain. Such a preparation would, therefore, be more acceptable to patients requiring long-term treatment.

Specifically, patients using doxepin, doxepin hydrochloride or their metabolites in a medicament formulated for topical application, optionally in conjunction with capsaicin or a compound that causes release of substance P from C-fibre afferent neurones, or reversibly depletes stores of substance P, prepared in accordance with the present invention, as an analgesic would not experience the side effects, including drowsiness, which are associated with an oral preparation of doxepin.

In preferred embodiments, the medicament prepared in accordance with the present invention is for use in ameliorating pain in an individual suffering from neuropathic pain, preferably chronic neuropathic pain. It is to be understood that such pain is characterised by symptoms including shooting, burning, numbness, paraesthesia/dyaesthesia (tingling) and allodynia. In particular chronic neuropathic pain is characterised by the presence of three of these five associated constituent symptoms. Preferably, the mean duration of the pain suffered by individuals to be treated is 69 months.

In preferred embodiments, the medicament prepared in accordance with the invention can be for long term use. Long term means more than 8 days use of the medicament, and includes treatment of many months duration, if not longer.

In preferred embodiments, the use of the medicament prepared in accordance with the current invention is not associated with the significant side effects which are normally associated with oral administration of a TCA. These side effects include drowsiness. Preferably, the medicament made in accordance with the current invention is for use in individuals who have previously had treatment failure with oral TCAs (either lack of analgesic effect or intolerable side effects).

Preferably, the medicament prepared in accordance with the current invention comprises between 2.5 and 7.5% doxepin hydrochloride but, more preferably, 5% doxepin hydrochloride. In the invention according to its fourth or fifth aspects, the medicament preferably comprises between 0.01 to 0.1 %, preferably between 0.015 and 0.075%, and, more preferably, between 0.015 and 0.035% capsaicin. In an especially preferred embodiment, the medicament comprises 3.3 % doxepin and 0.025 % capsaicin.

An advantage of those aspects of the present invention in which doxepin, doxepin hydrochloride and their metabolites are used in the preparation of a medicament for use as an analgesic, either with or without capsaicin, is that doxepin and doxepin hydrochloride are known compounds, with a history of use in individuals suffering from depression or pruritis. Thus, rather than developing a new compound specifically for use as an analgesic in the treatment of chronic pain, the present invention relates to the use of a known drug, with a well recognised spectra of possible side effects and contraindications, in a new application.

In a randomised, double blind, placebo controlled study, the effect of twice daily application of doxepin hydrochloride 5% was compared with placebo in forty patients with neuropathic pain. The details of this study are set out in Example 1 below. The results show that there was a significant reduction in pain scores in those treated with topical doxepin hydrochloride when compared to placebo. Minor

side effects were seen in 3 patients. There was no significant difference in the drowsiness levels in the two groups.

In another randomised, double blind, placebo controlled study, the effects of daily application of creams containing doxepin hydrochloride 3.3%, capsaicin 0.025%, and a mixture of doxepin hydrochloride 3.3% and capsaicin 0.025%, were compared with placebo in two hundred patients with neuropathic pain. The details of this study are set out in Example 2 below. The results show that there was a significant reduction in pain scores in those treated with topical doxepin hydrochloride, topical capsaicin and a combination of topical doxepin hydrochloride and capsaicin, when compared to placebo. The results also show that the onset of pain relief with the combination of topical doxepin hydrochloride and capsaicin was more rapid that that with doxepin hydrochloride or capsaicin alone. Minor side effects were seen in a relatively small number of patients.

Thus, doxepin hydrochloride has an analgesic effect in neuropathic pain and, when applied topically, is not commonly associated with side effects.

The apparent effect in the absence of central nervous system side effects may point to a peripheral site of action of doxepin. However, the half life of doxepin after single oral dose is almost 18 hours and that of its principle active metabolite desmethyldoxepin is 34 hours with time to steady state concentration after multiple dosing of around two weeks [28]. This two weeks to steady state would equate with the gap between initiation of topical treatment and first signs of analgesic effect and may suggest a systemic effect. Moreover, this may suggest that a metabolite may be active. The mode of action of capsaicin in enhancing the rate of onset of ananlgesia caused by TCAs such as doxepin is not fully understood.

The fact that the treatment population had a mean duration of pain of 69 months and that many had previous treatment failure with oral TCAs (either lack of analgesic effect or intolerable side effects) makes the results obtained more noteworthy and emphasises that the aim of treatment is to improve quality of life, itself a balance between effect and side effects of medication.

EXAMPLE 1

A randomised, double blind, placebo controlled study.

Subjects:

Forty adult patients attending a Pain Clinic with chronic neuropathic pain (presence of three of the five associated constituent symptoms of shooting, burning, numbness, paraesthesia/diasthesia and allodynia) unresponsive to codeine-based analgesics and non steroidal anti inflammatory drugs. All patients gave informed written consent and Regional Ethical Committee Approval was obtained. Patients taking oral antidepressants were excluded from the study. Those with a previous failed trial of oral TCAs were not excluded. Patients were allocated to one of two groups (A and B) using a computer generated random number list.

Study medication:

Doxepin hydrochloride 5% (Xepin cream, Bioglan Laboratories Ltd., Hitchen, England) (a white odourless cream) and aqueous cream (placebo).

Study design:

Randomised, double-blind placebo controlled. Patients in each group were instructed to apply a volume of cream equal to the size of a grain of rice to the painful area twice daily over a four week study period. Patients in group A received doxepin, those in group B placebo.

Measurements:

Patients were asked to record daily their average pain score (0-10 scale) and their level of drowsiness (again using a 0-10 scale) for the previous 24 hours for the 28 day study period. Patients were also asked to record adverse effects of cream application.

Data analysis:

Comparison of pain scores between the two groups both at the start and end of treatment were achieved using a parametric t-test. The difference between start and finish of treatment in the two groups was again with a t-test. $P<0.05$ was considered statistically significant.

Results:

Thirty patients provided results (75%) – 16 in the doxepin group, 14 in the placebo group. The mean age of all patients was 52 years (range 27 to 80) and mean duration of pain 69 months (range 3 to 324 months) with no statistically significant differences between the active and placebo treatment groups. There was no statistically significant difference in the average pain scores during the first week of treatment in either group. However, in the final 10 days of treatment, the average pain scores were significantly less ($p<0.05$) in the doxepin group (Table 1). When the differences between the start and end of treatment were compared there was no significant change in the placebo group: however, in the doxepin group there was a mean fall of 1.18 ($p<0.01$) (Table 2). One patient reported transient burning discomfort after cream application. There were no differences in the level of drowsiness between the two groups.

EXAMPLE II

Subjects:

This is a randomised, double-blind, placebo controlled study of 200 adult patients with chronic neuropathic pain. Ethical Committee approval was granted and written informed consent obtained from the study patients. For the purposes of this study, neuropathic pain was diagnosed when patients presented with pain which included at least 3 of the constituent symptoms of neuropathic pain, namely shooting pain, burning, numbness, pareasthesiae and sensitivity (allodynia). All patients had pain that was unresponsive to simple or compound codeine containing analgesics or non-steroidal anti-inflammatory drugs. All patients had tried oral TCAs for their pain and had either been unresponsive or intolerant. Patients were excluded if they had a known sensitivity to doxepin or capsaicin or if they had broken skin over the area where they felt their pain. Patients were asked to record all study measurements for one week prior to randomisation to provide baseline scores for these parameters. After baseline measurement, patients were randomly

allocated, using a computer generated random number list, in equal numbers, to the four study groups (A, B, C, D).

Study medication:

Patients in group A received placebo (aqueous cream), group B 3.3% doxepin hydrochloride (2 parts 5% doxepin hydrochloride (Xepin, Bioglan Laboratories Ltd) with 1 part aqueous cream), group C 0.025% capsaicin (Zacin, Elan Pharma)and group D 3.3% doxepin/0.025% capsaicin (1 part 0.075% capsaicin (Axsain, Elan Pharma) to 2 parts 5% doxepin (Xepin, Bioglan Laboratories Ltd). All study creams were white, odourless, had a similar non-greasy texture and they were contained in identical screw top containers marked with the appropriate randomisation letter. All cream combinations appeared to mix readily, further investigation is required to assess the stability of the mixtures in terms of physical and chemical compatibility.

Study design:

Patients were instructed to apply a volume of cream approximately equal in size to a grain of rice 3 time daily to the painful area and to record all study measurements daily for the 4 week study period. A visual representation of the amount of cream to be applied was used to assist concordance. Patients were asked not to wash the application area for one hour after application, and to ensure that they did wash the application finger to avoid accidental application of study cream elsewhere. At the end of the study period patients were asked to return their study cream container as a check on compliance. If an insufficient volume of cream had been used (arbitrarily set at 50% of contents of container) then these patients were excluded from the study.

Measurements:

Patients were asked to record the average level over the previous 24 hours of the following variables using a continuous 0-10 visual analogue score (VAS) which was measured to the nearest 0.1cm: overall pain, shooting pain, burning pain, numbness, pareasthesia and sensitivity. In addition, they were asked to record side-effects and their desire to stay on the study medication.

Data: Analysis:

Average changes in score with standard deviation and 95% Confidence Limits (95% C.L.) were calculated for the pre-study week and each of the four study weeks. The significance of changes from baseline levels were assessed using Students t test with $p<0.05$ being considered significant. Pre-study calculations suggested that 60 patients per group were required to show a 1 point fall (90% power, and 17 to demonstrate a 2 point fall (90% power).

Results:

No study subjects were excluded due to known sensitivity to doxepin or capsaicin. One hundred and fifty one patients (75.5%) provided results (41 placebo, 41 doxepin, 33 capsaicin, 36 doxepin/capsaicin). Non-compliance (less than 50% of cream used) was suspected in 18 patients (3 placebo, 2 doxepin, 8 capsaicin, 5 doxepin/capsaicin). Demographic details are shown in table 3. The duration of pain in the doxepin/capsaicin group was greater than the other groups ($p=0.05$).

The data for all pain scores was normally distributed and hence parametric tests were used. There were no statistically significant differences in baseline scores for the parameters measured between the treatment groups: pre-treatment overall pain scores were 7.13 in the placebo group, 7.29 in the doxepin group, 7.11 in the capsaicin group and 7.47 in the doxepin/capsaicin group. Overall pain was unchanged in the placebo group, but fell by 0.9 (95% C.L. 0.34-1.46) in the doxepin group ($p<0.001$), 1.12 (95% C.L. 0.44-1.8) in the capsaicin group ($p<0.001$) and 1.07 (95% C.L. 0.39-1.75) in the doxepin/capsaicin group ($p<0.001$). Statistically significant falls in pain scores were apparent in all three active treatment groups from week 2 of treatment (Figure 1).

Numbness and pins and needles did not change from baseline measurements in any of the four groups (Figures 2 and 3).

Scores for burning pain remained at baseline levels of 2.34 in the placebo group but increased in the doxepin group by 2.1 (95% C.L. 1.62 to 2.58) after 1 week ($p<0.001$) with a decrease from this elevated level by 0.68 (95% C.L. 0.32 to 1.04) by week 4 ($p<0.01$). There was a similar elevation from baseline in the capsaicin group by 1.6 (95% C.L. 0.86 to

2.34) after the first week of treatment ($p<0.01$), with a gradual decrease by 0.52 (95% C.L. -0.42 to 1.46) after the fourth treatment week. In the doxepin/capsaicin group the elevation from baseline was less substantial, rising by 0.32 after one week (95% C.L. 0.11 to 0.53) ($p<0.01$). There was no decrease in this level as treatment time increased Figure 4). Sensitivity was unchanged by placebo or doxepin. Scores for sensitivity fell from the baseline immediately after commencement of capsaicin treatment, with an initial fall of 1.2 (95% C.L. 0.1 to 2.3) after the first study week ($p<0.001$), with a further gradual further fall by 0.19 (95% C.L. -0.49 to 0.87) by week 4 ($p<0.05$). In the doxepin/capsaicin group there was an immediate fall from baseline level by 0.95 (95% C.L. 0.7 to 1.2) after the first study week ($p<0.01$) with no further falls with continued treatment (Figure 5). Shooting pain was unaltered by placebo or doxepin. Application of capsaicin reduced shooting pain from baseline level by 0.75 (95% C.L. 0 to 1.5) after 4 weeks ($p<0.001$). Shooting pain was reduced by 0.73 (95% C.L. 0.28 to 1.18) with the doxepin/capsaicin combination ($p<0.001$) (Figure 6).

In terms of cream preference, it emerged when blinding codes were broken that 1 patient (2.4%) wished to continue with placebo, 17(41%) with doxepin, 13(39%) with capsaicin and 9 (25%) with doxepin/capsaicin.

Side effects were minor. Four patients (97%) in the doxepin and 2(5.5%) in the doxepin/capsaicin group complained of drowsiness, 1 (2.4%) had a skin rash with doxepin, 1, (2.8%) a headache with doxepin/capsaicin and 2(4.9% had itch with doxepin. Burning discomfort after cream application was noted by 27 (81%) in the capsaicin group, 22 (61%)in the doxepin/capsaicin group and 4(17%) in the doxepin group.

References

1. McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. *BMJ* 1996; **68**: 217 - 27.

2. Max MB, Culnane M, Schafer SC et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology* 1987; **37**: 589 - 96.

3. Watson CP, Evans RJ. A comparative trial of amitriptyline and zimelidine in post-herpetic neuralgia. *Pain* 1985; **23**: 387 - 94.

4. Max MB, Schafer SC, Culnane M, Smoller B, Dubner R, Gracely RH. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. *Neurology* 1988; **38**: 1427 - 32.

5. Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith L, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. *Neurology* 1982; **32**: 671 - 3.

6. Kishore-Kumar R, Max MB, Schafer SC et al. Desimipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther* 1990; **47**: 305 - 12.

7. Max MB, Kishore-Kumar R, Schafer SC et al. Efficacy of desimipramine in painful diabetic neuropathy: a placebo-controlled trial. *Pain* 1991; **45**: 3 - 9.

8. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desimipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992; **326**: 1250 - 6.

9. Sindrup SH, Gram LF, Skjold T, Grodum E, Brosen K, Beck-Nielsen H. Clomipramine vs desimipramine vs placebo in the treatment of diabetic neuropathy symptoms. A double-blind cross-over study. *Br J Clin Pharmacol* 1990; **30**: 683 - 91.

10. Langohr HD, Stohr M, Petruch F. An open and double-blind cross-over study on the efficacy of clomipramine (Anafranil) in patients with painful mono- and polyneuropathies. *Eur Neurol* 1982; **21**: 309 - 17.

11. Kvinesdal B, Molin J, Froland A, Gram LF. Imipramine treatment of painful diabetic neuropathy. *JAMA 1984*; **251**: 1727 - 30.

12. Lund A, Mjellem-Joly N, Hole K. Chronic administration of desimipramine and zimelidine changes the behaviour response in the formalin test in rats. *Neuropharmacology* 1991; **30**: 481 - 7.

13. Acton J, McKenna JE, Melzack R. Amitriptyline produces analgesia in the formalin pain test. *Experimental Neurology* 1992; **117**: 94 - 6.

14. Bianchi M, Rossoni G, Sacerdote P, Panerai AE, Berti F. Effects of clomipramine and fluoxetine on subcutaneous carrageenin-induced inflammation in the rat. *Inflamm Res* 1995; **44**: 466 - 9.

15. Michelson D, Misiewicz-Poltorak B, Raybourne RB, Gold PW, Sternberg EM. Imipramine reduces the local inflammatory response to carrageenin. *Agents Actions* 1994; **42**: 25 - 8.

16. Sawynok J, Reid AR, Esser MJ. Peripheral antinociceptive action of amitriptyline in the rat formalin test: involvement of adenosine. *Pain* 1999; **80**: 45 - 55.

17. Turnbull A. Tincture of capsicum as a remedy for chilblains and toothache. *Dublin Med Press* 1850; **95**: 6 - 7.

18. Bernstein JE, Korman NJ, Bickers DR, Dahl MV, Millikan LE. Topical capsaicin treatment of chronic postherpetic neuralgia. *J Am Acad Dermatol* 1989; **21**: 265 - 70.

19. Watson CP, Tyler KL, Bickers DR, Millikan LE, Smith S, Coleman E. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. *Clin Therapeutics* 1993; **15**: 510 - 25.

20. Watson CP, Evans RJ, Watt VR. Post-herpetic neuralgia and topical capsaicin. *Pain* 1988; **33**: 333 - 40.

21. The Capsaicin Study Group. Treatment of painful diabetic neuropathy with topical capsaicin. A multicenter, double-blind, vehicle-controlled study. *Arch Intern Med* 1991; **151**: 2225 - 9.

22. Capsaicin Study Group. Effect of treatment with capsaicin on daily activities of patients with painful diabetic neuropathy. *Diabetes Care* 1992; **15**: 159 - 65.

23. Ellison N, Loprinzi CL, Kugler J et al. Phase III placebo-controlled trial of capsaicin cream in the management of surgical neuropathic pain in cancer patients. *J Clin Oncology* 1997; **15**: 2974 - 80.

24. Rains C, Bryson HM. Topical Capsaicin. A review of its pharmacological properties and therapeutic potential in post-herpetic neuralgia, diabetic neuropathy and osteoarthritis. *Drugs & Ageing* 1995; 7 : 317 - 28.

25. McCleane GJ. Topical doxepin hydrochloride reduces neuropathic pain: a randomised, double-blind, placebo controlled study. *The Pain Clinic*: In press

26. Drake LA, Millikan LE. The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitis. Doxepin Study Group. Arch Dermatol 1995; 131: 1403 - 8.

27. Drake LA, Fallon JD, Sober A. Relief of pruritis in patients with atopic dermatitis after treatment with topical doxepin cream. The Doxepin Study Group. J Am Acad Dermatol 1994; 31: 613 - 6.

28. Faulkner RD, Pitts WM, Lee CS, Lewis WA, Fann WE. Multiple-dose doxepin kinetics in depressed patients. *Clin Pharmacol Ther* 1983; **34**: 509 - 15.

Table 1

Average pain scores at start and end of treatment period

Treatment period	N	Mean	Standard deviation	Std. Error mean	95% confidence interval of mean lower Upper
Average pain score first week of study	placebo 14	6.49	1.98	0.53	-1.44 1.98
	doxepin 16	6.22	2.51	0.63	
Average pain score in last 10 days of treatment	placebo 14	6.91	2.15	0.57	* 6.7E-2 3.67
	doxepin 16	5.04	2.61	0.65	

• $p < 0.05$

Table 2

Change of pain scores from start to end of treatment period

Treatment group (N)	Mean fall in pain score	Standard deviation	Standard error mean	95% confidence limits: lower	95% confidence limits: upper
placebo (14)	-0.42	1.4	0.37		
				-2.92	-0.29
doxepin (16)	1.18*	2.01	0.5		

• $p < 0.01$

Table 3

Demographic Details

Mean (S.Dev)

	Placebo	Doxepin	Capsaicin	Doxepin / Capsaicin
Age (years)	45.4 (13.6)	47.8 (17.2)	47.8 (27.8)	43.6 (12.9)
Duration of pain (months)	57.9 (54.6)	59.6 (62.3)	59.4 (47.9)	74.9 (66.3)
Male / Female	16 / 25	20 / 21	13 / 20	14 / 22

Claims

1. Use of doxepin, doxepin hydrochloride or a metabolite of doxepin or doxepin hydrochloride for the manufacture of a medicament for ameliorating pain in an individual.

2. Use of a TCA for the manufacture of a medicament for ameliorating pain in an individual, wherein the medicament is formulated for topical application.

3. A use as claimed in claim 2, wherein the TCA is amitriptyline, imipramine, desipramine or clomipramine.

4. A use as claimed in claim 2, wherein the TCA is doxepin, doxepin hydrochloride or a metabolite of doxepin or doxepin hydrochloride.

5. A use as claimed in any of the preceding claims, wherein the side effects normally associated with oral administration of a TCA are reduced or absent.

6. A use as claimed in any of the preceding claims, wherein the individual has previously had treatment failure with an oral TCA.

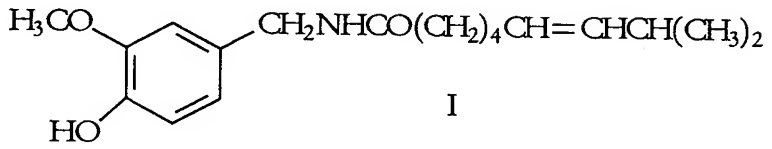
7. A use as claimed in any of the preceding claims, wherein the medicament further comprises a compound capable of causing release of substance P from C- fibre afferent neurones.

8. A use as claimed in any of the preceding claims, wherein the medicament further comprises a compound capable of causing local depletion of substance P from C-fibre afferent neurones.

9. A use as claimed in claim 7 or claim 8, wherein the amelioration of pain in the individual has a rapid onset.

10. A use as claimed in claim 9, wherein the onset occurs in two weeks or less.

11. A use as claimed in any of claims 7 to 10, wherein the medicament further comprises a compound of formula I:



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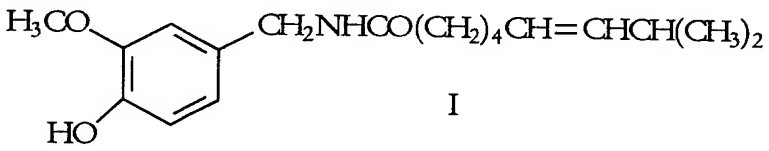
12. A use as claimed in claim 11, wherein the compound of formula I is capsaicin.

13. A use as claimed in any of the preceding claims, wherein the medicament further comprises a pharmaceutically active carrier rendering it suitable for topical application, preferably to the skin.

14. A use as claimed in any of the preceding claims, wherein the medicament is formulated for topical application at or in the vicinity of the source of pain or the perceived origin of the pain.

15. Use of a TCA and a compound of formula I



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for the manufacture of a medicament for ameliorating deep seated or internal pain or discomfort in an individual, wherein the TCA has an ameliorating effect upon said pain.

16. A use as claimed in any of the preceding claims, wherein the pain in an individual is neuropathic pain, preferably chronic neuropathic pain.

17. A use as claimed in any of the preceding claims, wherein the mean duration of the pain suffered by an individual to be treated is 69 months.

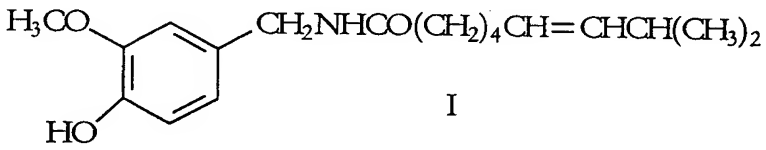
18. A use as claimed in any of the preceding claims, wherein the individual requires long term treatment.

19. A use as claimed in any of the preceding claims, wherein the medicament comprises between 2.5 to 7.5 % and, preferably, 5 % doxepin hydrochloride.

20. A use as claimed in any of the preceding claims, wherein the medicament comprises between 0.01 to 0.1 %, preferably between 0.015 and 0.075%, and, more preferably, between 0.015 and 0.035% capsaicin.

21. A use as claimed in claim 20, wherein the medicament comprises 3.3 % doxepin and 0.025 % capsaicin.

22. A pharmaceutical composition comprising a TCA and a compound of formula I:



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23. A pharmaceutical composition as claimed in claim 22, for use as an analgesic.

24. A pharmaceutical composition as claimed in claim 22 or claim 23, for topical application at or in the vicinity of a source of pain or discomfort.

25. A pharmaceutical composition as claimed in any of claims 22 to 24, further comprising a pharmaceutical carrier and suitable for topical application to the skin.

26. A pharmaceutical composition as claimed in any of claims 22 to 25, for ameliorating deep seated or internal pain.

27. A pharmaceutical composition as claimed in any of claims 22 to 26, for ameliorating skeletal, muscular or joint pain.

28. A pharmaceutical composition as claimed in any of claims 22 to 27, for ameliorating neuropathic pain, particularly painful diabetic neuropathy or post-herpetic neuralgia.

29. A pharmaceutical composition as claimed in any of claims 22 to 28, wherein the TCA is present in an amount sufficient to reduce burning discomfort associated with the application of a compound of formula I to the skin.

30. A pharmaceutical composition as claimed in any of claims 22 to 29, wherein the compound of formula I is present in an amount sufficient to augment an analgesic effect provided by the TCA.

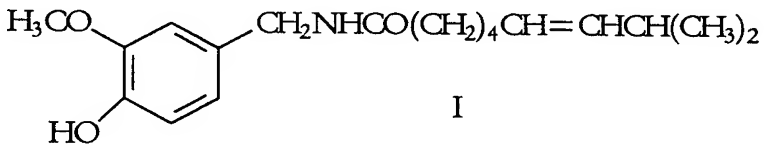
31. A pharmaceutical composition as claimed in any of claims 22 to 30, wherein the compound of Formula I is capsaicin.

32. A pharmaceutical composition as claimed in any of claims 22 to 31, in the form of a cream, jelly ointment, gel, lotion, paste or for application by a patch.

33. A method of providing an analgesic treatment comprising administering doxepin, doxepin hydrochloride or a metabolite of doxepin or doxepin hydrochloride to a patient in need of analgesic treatment.

34. A method as claimed in claim 33, wherein doxepin, doxepin hydrochloride or a metabolite of doxepin or doxepin hydrochloride is administered topically to a patient in need of analgesic treatment

35. A method of providing an analgesic treatment comprising sequentially or simultaneously administering a TCA and a compound of formula I



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to a patient in need of analgesic treatment.

36. A method as claimed in claim 35, wherein the TCA and compound of formula I are topically applied to the skin at or in the vicinity of a source of pain.

37. A method as claimed in claim 36, wherein the TCA and compound of formula I are applied simultaneously in a single preparation comprising the TCA, compound of formula I and a pharmaceutically acceptable carrier.

38. A method as claimed in claim 37, wherein said preparation is a cream, jelly, ointment, gel, lotion, paste or for application by a patch.

39. A method as claimed in any of claims 35 to 38, wherein the analgesic treatment is to ameliorate a deep seated or internal pain.

40. A method as claimed in any of claims 35 to 39, wherein the analgesic treatment is to ameliorate skeletal, muscular or joint pain.

41. A method as claimed in any of claims 35 to 39, wherein the analgesic treatment is to ameliorate neuropathic pain, particularly painful diabetic neuropathy or post herpetic neuralgia

42. A method as claimed in any of claims 35 to 41, wherein the TCA is used in an amount sufficient to reduce burning discomfort associated with the application of a compound of formula I.

43. A method as claimed in any of claims 35 to 42, wherein the TCA is used in an amount sufficient to augment an analgesic effect provided by the compound of formula I.

44. A method as claimed in any of claims 35 to 43, wherein the compound of formula I is capsaicin.

45. A method of ameliorating deep seated or internal pain, comprising topically administering a TCA to a subject suffering said pain at or in the vicinity of the source of said pain.

46. A method as claimed in claim 45, wherein the TCA is applied to the skin.

47. A method as claimed in claim 45 or claim 46, wherein the pain is skeletal, muscular or joint pain.

48. A method as claimed in claim 47, wherein the pain is neuropathic pain, particularly painful diabetic neuropathy or post herpetic neuralgia

49. A method as claimed in any of claims 45 to 48, wherein the TCA is administered with a pharmaceutically acceptable carrier.

50. A method as claimed in claim 49, wherein the TCA is administered in a cream, jelly, ointment, gel, lotion, paste or for application by a patch.

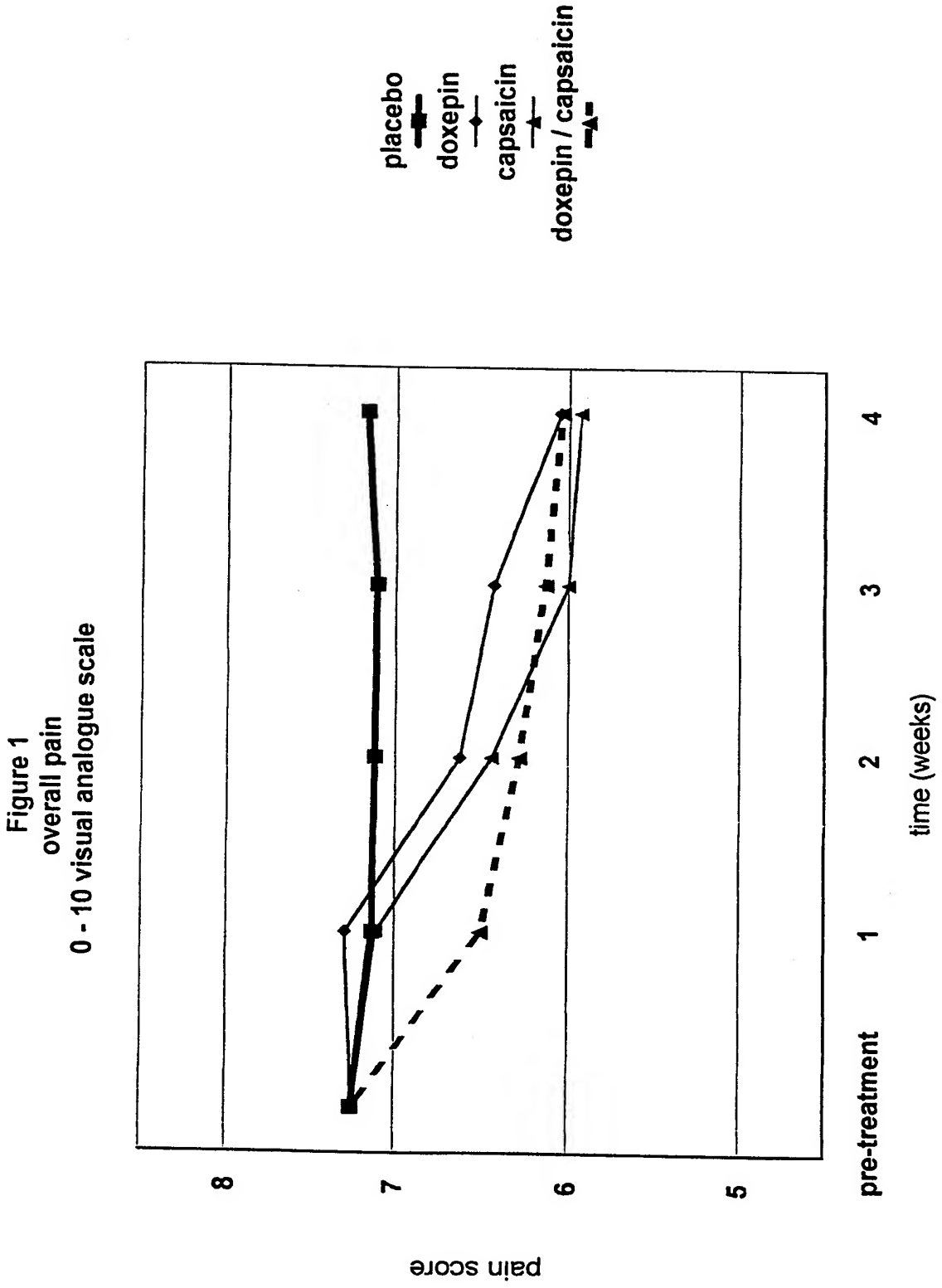

Figure 1
overall pain
0 - 10 visual analogue scale

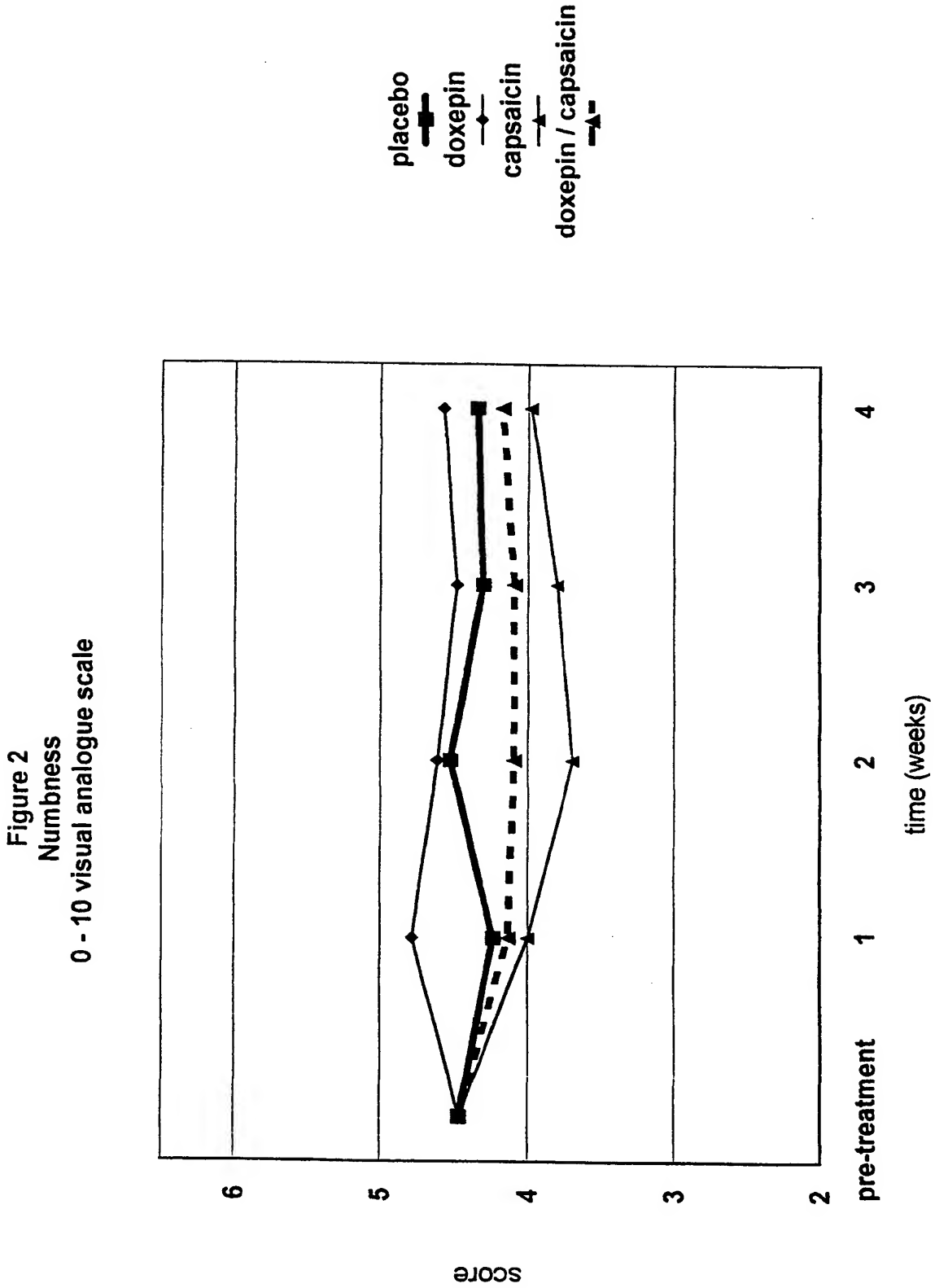

Figure 2
Numbness
0 - 10 visual analogue scale

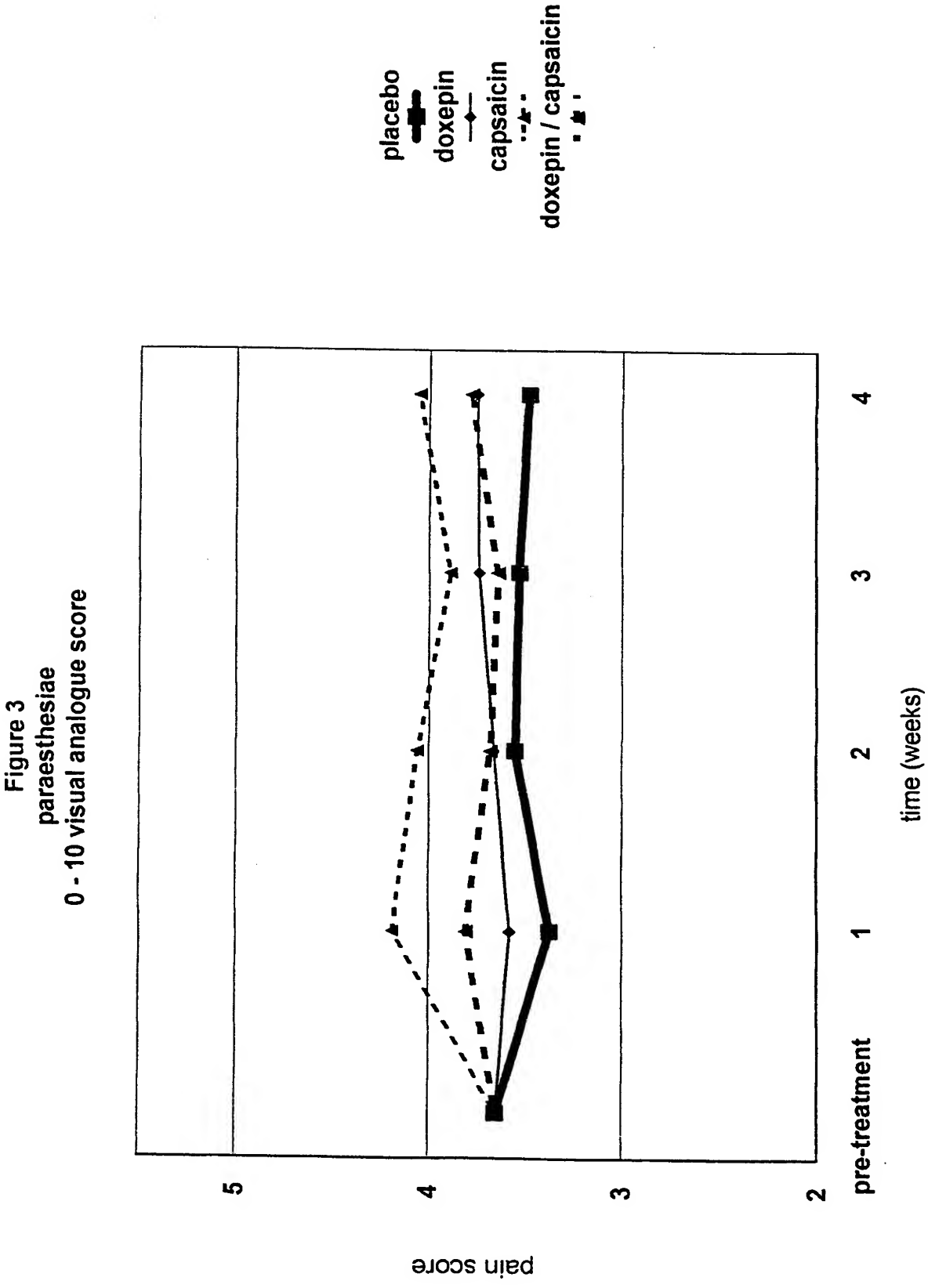

Figure 3
paraesthesiae
0 - 10 visual analogue score

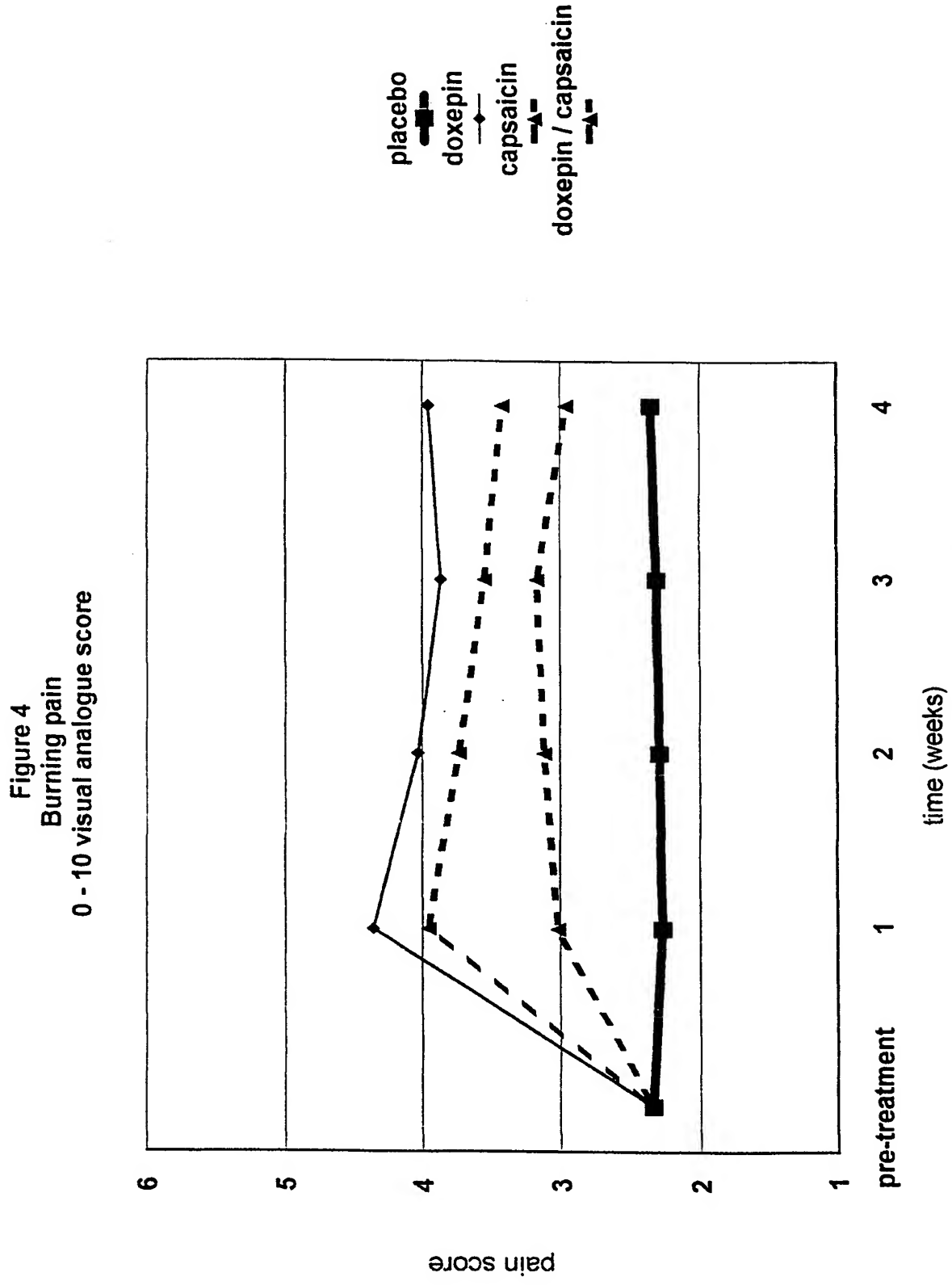

Figure 4
Burning pain
0 - 10 visual analogue score

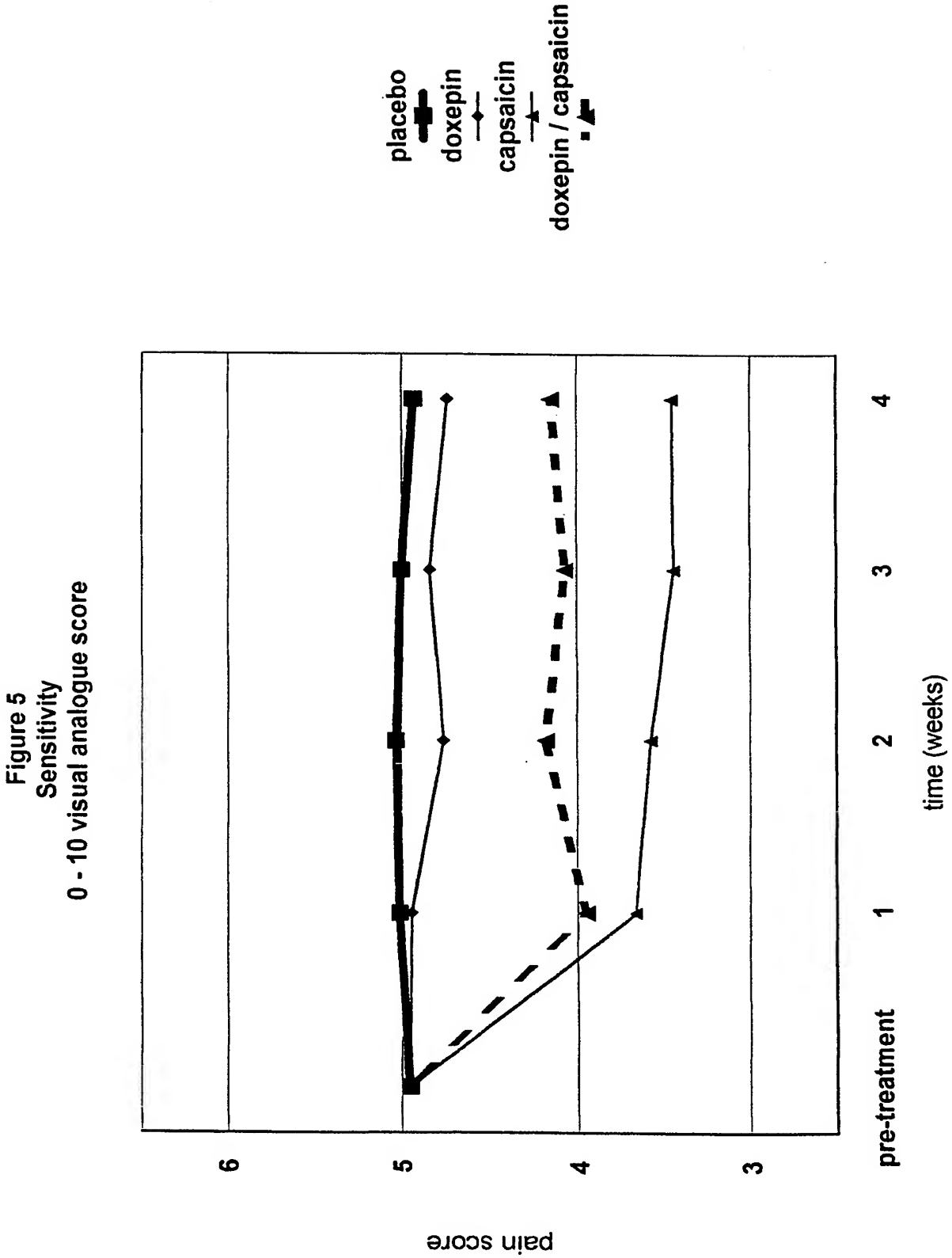

Figure 5
Sensitivity
0 - 10 visual analogue score

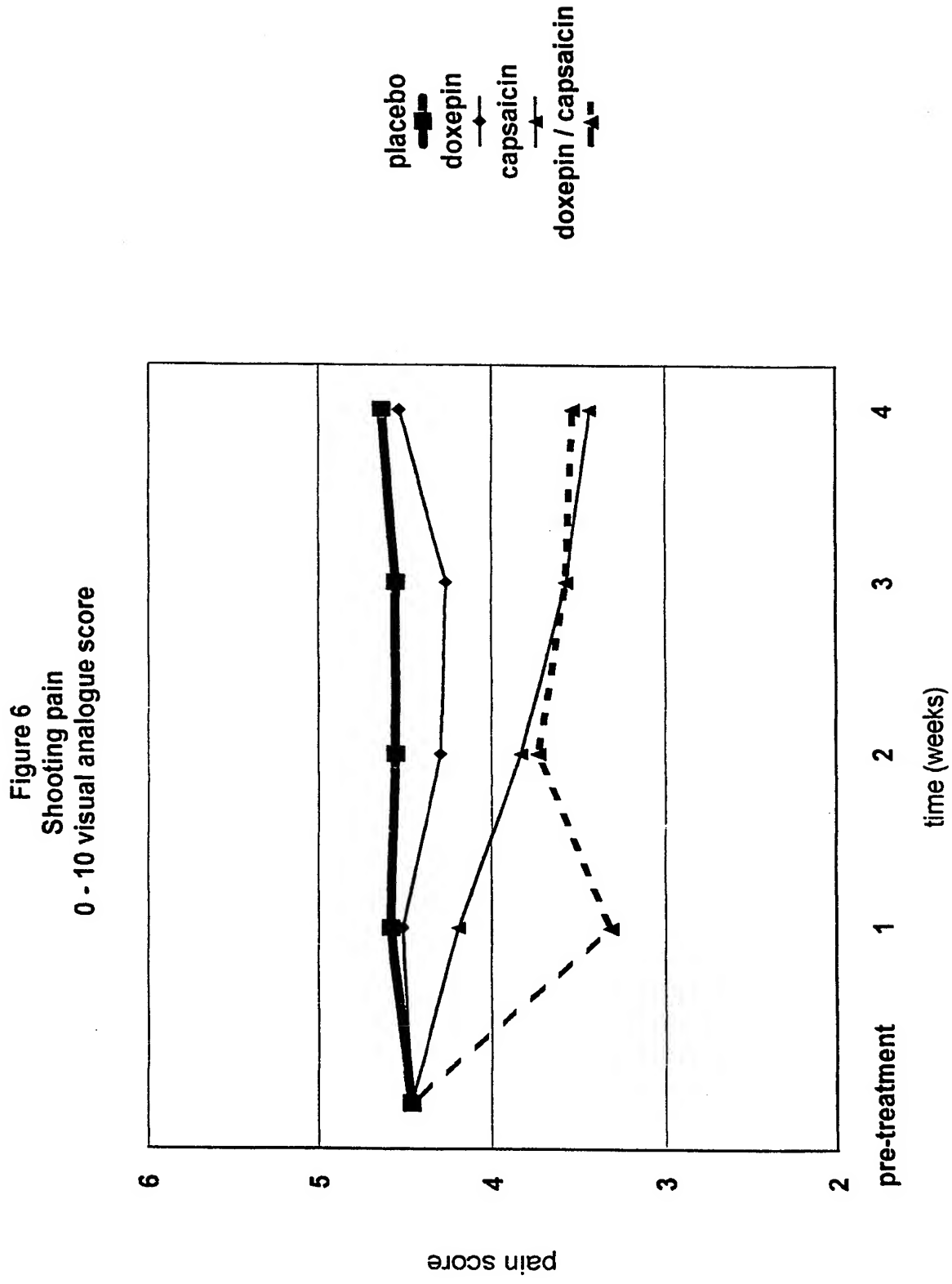

Figure 6
Shooting pain
0 - 10 visual analogue score

INTERNATIONAL SEARCH REPORT

Internat I Application No
PCT/GB 00/00640

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/165 A61P43/00 A61K31/645 //(A61K31/645,31:165)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 10815 A (FROME BRUCE M) 27 March 1997 (1997-03-27) page 1 page 11 page 17 page 20 page 28 page 9 page 31	2,3,5,6, 13,14, 16-18, 45,46, 48-50
Y	claims 5,9,11	1-50

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
7 June 2000	15/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Brunnauer, H

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 008 289 A (BERNSTEIN JOEL E) 16 April 1991 (1991-04-16) claims 1,3,6	1,2, 4-14, 17-20, 22-24, 26-31, 33-35, 42-44
Y	GALER B.S.: "Neuropathic pain of peripheral origin: Advances in pharmacologic treatment." NEUROLOGY, (1995) 45/12 SUPPL. 9 (S17-S25). , XP000909402 page 22, left-hand column page 20, left-hand column	1-50
Y	EMANUELE N.V. ET AL: "Diabetic neuropathy: Therapies for peripheral and autonomic symptoms." GERIATRICS, (1997) 52/4 (40-50). , XP000090304 page 42 page 45	1-50
Y	VOLMINK J (REPRINT) ET AL: "TREATMENTS FOR POSTHERPETIC NEURALGIA - A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS" FAMILY PRACTICE, (FEB 1996) VOL. 13, NO. 1, PP. 84-91. ISSN: 0263-2136., XP000887093 UNIV OXFORD, RADCLIFFE INFIRM, DEPT PUBL HLTH & PRIMARY CARE, GIBSON BLDG, OXFORD OX2 6HE, ENGLAND (Reprint) abstract page 86 -page 88	1-50
A	BERBERIAN B J ET AL: "The addition of topical doxepin to corticosteroid therapy: an improved treatment regimen for atopic dermatitis." INTERNATIONAL JOURNAL OF DERMATOLOGY, (1999 FEB) 38 (2) 145-8. , XP000909356 abstract page 140; tables 1,2 page 147	1-50
P,X	WO 99 59598 A (ESSER MIKE ;REID ALLISON (CA); SAWYNOK JANA (CA); UNIV DALHOUSIE () 25 November 1999 (1999-11-25) claims 1,2,20,21,25,27	2,3,5,6, 13,14, 16-18, 45,46, 48-50

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna al Application No
PCT/GB 00/00640

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9710815 A	27-03-1997	NONE	
US 5008289 A	16-04-1991	US 5134166 A	28-07-1992
WO 9959598 A	25-11-1999	AU 3807799 A	06-12-1999